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STATE-OF-THE-ART PAPER

Reperfusion Strategies for Acute Myocardial Infarction in the Elderly

Benefits and Risks

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The optimal reperfusion strategy in elderly patients with ST-segment elevation myocardial infarction (STEMI) remains a topic of debate. This lack of consensus stems from the exclusion or under-representation of the elderly in clinical trials. This review evaluates the available literature pertaining to reperfusion therapy for the treatment of STEMI in the elderly. We identified all published studies evaluating the effectiveness of thrombolytic therapy, primary percutaneous coronary intervention (PCI), or adjunctive therapies to reperfusion by conducting an electronic search of MEDLINE through December 2003. Meta-analysis of clinical trials suggests a survival benefit of thrombolytic therapy in the elderly with STEMI, whereas some observational studies have raised concerns about the lack of short-term benefit or possibility of harm with thrombolysis. However, most observational studies demonstrate improved intermediate-term survival with thrombolysis. In contrast, multiple clinical trials and observational studies indicate improved survival and low risk of stroke with primary PCI compared with thrombolysis in elderly patients with STEMI. Information on the efficacy of newer antithrombotic agents as adjunct to thrombolysis or primary PCI is scarce. Available data suggest an increased risk of intracerebral bleeding with the combination of a fibrin-specific agent and a glycoprotein IIb/IIIa receptor antagonist in patients >75 years of age. Clearly targeted large-scale clinical trials are needed to evaluate the relative merits of available reperfusion strategies as well as newer antithrombotic adjunctive therapies in the elderly with STEMI. (J Am Coll Cardiol 2005;45:471–8) © 2005 by the American College of Cardiology Foundation

Despite the greater incidence and risk of ST-segment elevation myocardial infarction (STEMI) among older patients (1–3), several large randomized clinical trials evaluating reperfusion therapy for the treatment of these patients (3,4) or the relative merits of mechanical versus chemical reperfusion (5) have systematically excluded elderly patients. Even trials that have included older patients have substantially underrepresented them, with only 10% to 15% of the populations being >75 years of age (4,6–8). Thus, much less is known about the risk/benefits of reperfusion therapy or the optimal reperfusion strategy among the elderly with STEMI. The lack of data regarding reperfusion for STEMI in the elderly, combined with atypical symptoms, high levels of comorbidity, and delayed presentation, have all potentially contributed to the significant underutilization of such treatment in this cohort (2,9,10). Older age is one of the key predictors of failure to use reperfusion therapy in otherwise eligible patients (2,9,10). The proportion of "ideal" elderly patients receiving reperfusion therapy decreases as age increases (64.8%, 65 to 69 years; 60.1%, 70 to 74 years; 50.4%, 75 to 79 years; 35.4%, 80 to 84 years; 20.4%, ≥85 years) (10).

The main objective of this review is to evaluate the available literature pertaining to reperfusion therapy for the treatment of STEMI in the elderly. An extensive electronic search of MEDLINE through December 2003 was conducted in order to identify all published studies evaluating the effectiveness of fibrinolytic therapy, percutaneous coronary intervention (PCI), or adjunctive therapies to reperfusion for treatment of STEMI in the elderly. In addition to reviewing the reference list of each identified study, we examined existing bibliographies of relevant studies and review articles. Finally, we reviewed scientific session abstracts in *Circulation*, *Journal of the American College of Cardiology*, and *European Heart Journal* through December 2003.

INTRAVENOUS THROMBOLYTIC THERAPY IN THE ELDERLY WITH STEMI

Intravenous thrombolysis remains the most common reperfusion strategy for the treatment of patients with STEMI. More recent trials and registries have provided important insights into the risks and benefits of thrombolysis in this high-risk cohort (2,6–9). Randomized clinical thrombolytic trials and registry data show that the risk of intracranial

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Abbreviations and Acronyms

ASSENT = Assessment of Safety and Efficacy of a New Thrombolytic trial
CI = confidence interval
HR = hazard ratio
MIR = Myocardial Infarction Registry
MITRA = Maximum Individual Therapy in Acute Myocardial Infarction trial
OR = odds ratio
PCI = percutaneous coronary intervention
RR = relative risk
STEMI = ST-segment elevation myocardial infarction

hemorrhage increases with age, more so with fibrin-specific agents than with nonspecific agents (6–8,11–12). Despite this increased risk, thrombolysis appears to be beneficial in decreasing mortality in the elderly (3).

Data from randomized clinical trials. The Fibrinolytic Therapy Trialists' collaborative group found that younger patients with STEMI have a slightly greater relative reduction in mortality compared with elderly patients, but the higher absolute mortality in the elderly results in higher absolute mortality reduction (3). Thus, a 26% reduction in mortality in patients <55 years of age resulted in 11 lives saved per thousand patients treated in this age group. In contrast, although there was only a 15% reduction in mortality in patients >75 years of age, this resulted in 34 lives saved per thousand patients treated in this age group (Fig. 1) (3,13). Similarly, White et al. (14) examined the effects of age on outcomes in patients enrolled in the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries-I (GUSTO-I) trial and found that the greatest absolute reduction in mortality with thrombolysis occurred in patients 65 to 85 years of age. Furthermore, the net benefit (mortality and/or disabling stroke) was greater with tissue plasminogen activator versus streptokinase. In contrast, the net benefit favored streptokinase among patients >85 years of age. However, because of the small number of patients >85 years of age enrolled in the trial (<1% of the study population), these investigators suggested using caution in making any firm conclusions from this data regarding efficacy of specific fibinolytic agents among patients in this age group.

Newer thrombolytic agents such as reteplase, tenecteplase, and lanoteplase have not been proven to be superior to tissue plasminogen activator in reducing mortality in STEMI patients. However, the Asessment of Safety and Efficacy of a New Thrombolytic (ASSENT) investigators demonstrated that, compared with bolus and infusion of tissue plasminogen activator, the increased fibrin-specific tenecteplase was associated with lower rates of major bleeding (15.15% vs. 8.33%) as well as intracranial hemorrhage (3.02% vs. 1.14%) in the high-risk cohort of elderly females >75 years of age and weighing <67 kg (15). In addition, when these investigators compared adjunctive heparin dosing of tenecteplase in the ASSENT-2 and -3 trials (doses of which were similar in the two studies), they found that the lower dose of weight-based heparin used in the ASSENT-3 trial was associated with lower major bleeding rates compared with the higher heparin dose used in the ASSENT-2 trial (adjusted odds ratio [OR] 0.49, 95% confidence interval [CI] 0.35 to 0.67), particularly in patients weighing <70 kg (16).

Data from observational registries. Some observational studies have raised concerns about the lack of short-term survival benefit or the possibility of harm with thrombolysis (17–19). Thiemann et al. (17) examined patients from the Cooperative Cardiovascular Project and found that while survival among patients receiving thrombolysis was better in those 65 to 75 years of age, it was significantly lower in those >75 years of age, particularly women. Angeja et al. (18) examined data from the National Registry of Myocardial Infarction-2 and found that, compared with patients receiving no reperfusion therapy, tissue plasminogen activator-treated patients had lower rates of in-hospital death and the composite of in-hospital death or stroke if they were <85 years of age, whereas no such benefit was observed among those ≥85 years of age. Similarly, Soumerai et al. (19) evaluated 2,659 patients ≥65 years of age admitted with STEMI to community hospitals in Minnesota between 1992 and 1996 and found that, compared with no reperfusion, thrombolytic therapy was associated with lower in-hospital mortality in eligible patients <80 years of age, but the odds of death increased 1.4-fold in those ≥80 years of age.

In contrast, other investigations have shown that, although there is no reduction in short-term mortality, intermediate-term mortality is significantly reduced by intravenous thrombolysis in this cohort. A combined analysis from the Maximum Individual Therapy in Acute Myocardial Infarction (MITRA) trial and Myocardial Infarction Registry (MIR) demonstrated that thrombolytic therapy had no impact on in-hospital mortality among patients aged ≥75 years of age, but was associated with a significant reduction in 18-month mortality when compared with no reperfusion (OR 0.58; 95% CI 0.39 to 0.88) (20). Similarly, in an analysis of patients >65 years of age, Berger et al. (21) showed no impact of thrombolysis on 30-day mortality

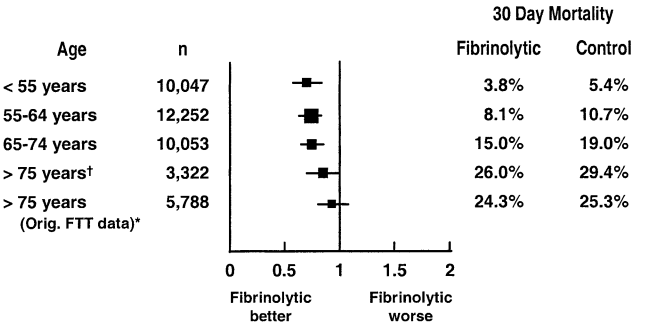

Figure 1. Benefits of thrombolytic therapy in different age groups. FTT = Fibrinolytic Therapy Trialists.

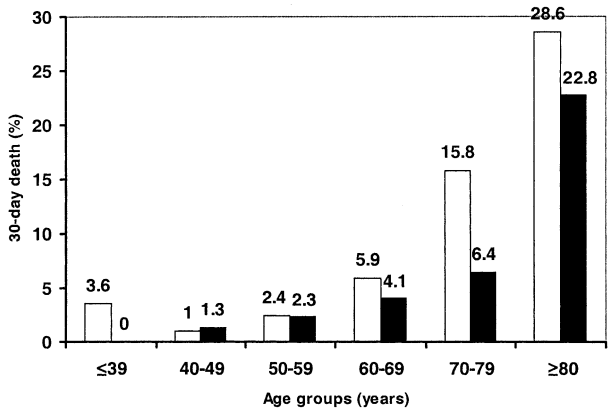

Figure 2. Thirty-day mortality in patients randomized to primary coronary angioplasty versus intravenous thrombolysis in the Primary Coronary Angioplasty Trialists' Overview. **Open bars** = lytic; **solid bars** = percutaneous coronary intervention.

(hazard ratio [HR] 1.01; 95% CI 0.94 to 1.09), but there was a significant association with lower mortality at one year (HR 0.84; 95% CI 0.79 to 0.89). The beneficial effect of intravenous thrombolysis was also reported by Stenestrand et al. (22) among Swedish STEMI patients ≥75 years of age, with a significant reduction in one-year mortality (relative risk [RR] 0.88; 95% CI 0.79 to 0.97).

INTRAVENOUS THROMBOLYSIS VERSUS PRIMARY PCI IN THE ELDERLY WITH STEMI

Data from randomized clinical trials. Many randomized trials have shown more favorable short-term outcomes in STEMI patients with the use of primary PCI rather than with thrombolytic therapy (5). However, these trials did not specifically evaluate elderly patients, thereby limiting the extrapolation of their findings to this cohort. Nevertheless, subset analysis in two trials suggested that primary PCI may be more effective than thrombolytic therapy in elderly patients (23,24). In the Primary Angioplasty in Myocardial Infarction study, 38% of patients enrolled were ≥65 years of age (23). This investigation showed a trend towards fewer deaths (5.7% vs. 15.0%; p = 0.066), lower rate of recurrent ischemia (8.6% vs. 20%; p = 0.048), and a lower composite rate of recurrent myocardial infarction and death (8.6% vs. 27.5%; p = 0.0003) in elderly patients who underwent angioplasty than in those who received thrombolytic therapy. The largest randomized trial, the Global Use of Strategies To Open occluded coronary arteries in acute coronary syndromes-IIb (GUSTO-IIb), also showed a trend towards lower 30-day mortality with primary PCI than with thrombolytic therapy among patients ≥70 years of age (24). The Primary Coronary Angioplasty Trialists investigators studied 2,635 patients enrolled in 10 randomized trials of primary angioplasty versus thrombolysis (25). They found that, as compared with thrombolysis, primary angioplasty was most effective in reducing mortality at 30 days among patients ≥70 years of age than in those <70 years (Fig. 2) (25).

A recently published very small trial randomly assigned patients aged >75 years with STEMI to receive either primary PCI (n = 47) or intravenous streptokinase (n = 41) and suggested a lower composite of death, reinfarction, or stroke at one year with primary PCI (13% vs. 44%; RR 0.19; 95% CI 0.06 to 0.59) (26). The 30-day (7% vs. 22%; RR 0.25; 95% CI 0.04 to 1.11) and 1-year mortality rates (11% vs. 29%; RR 0.29; 95% CI 0.07 to 1.00) were also lower in the primary PCI group.

Data from observational studies. Consistent with the findings of randomized clinical trials, four observational studies have suggested that primary PCI may result in lower mortality than thrombolytic therapy in elderly patients with STEMI (Fig. 3) (27–30).

Investigators from the Cooperative Cardiovascular Project evaluated 234,739 patients >65 years of age with STEMI (27). In the eligible cohort, 18,645 (23.2%) received thrombolysis, and 2,038 (2.5%) underwent primary PCI within 6 h of symptom onset. Patients treated with primary PCI had a lower one-year mortality rate (14.4% vs. 17.6%; adjusted HR 0.88; 95% CI 0.73 to 0.94). Among patients without any contraindications for reperfusion, there was a trend toward reduced 30-day mortality with primary PCI (10.1% vs. 12.0%; HR 0.84; 95% CI 0.68 to 1.03). Primary PCI was also associated with lower rates of reinfarction (4.0% vs. 5.3%; p = 0.009), cerebral hemorrhage (0.2% vs. 1.4%; p < 0.001), and other hemorrhagic end points (21.5% vs. 28.6%; p = 0.001).

The MITRA and MIR investigators did not restrict their analysis to elderly patients with STEMI, but a subgroup analysis of patients ≥65 years of age showed a progressively greater benefit of primary PCI over thrombolytic therapy with increasing age (28). Similarly, in a subgroup analysis of patients with STEMI age ≥75 years enrolled in the National Registry of Myocardial Infarction-2, Tiefenbrunn et al. (29) found a lower rate of combined end point of death and non-fatal stroke favoring primary PCI over alteplase (14.6% vs. 18.4%, p = 0.03). Finally, Mehta et al. (30) analyzed 2,975 patients ≥70 years of age with STEMI enrolled in the Global Registry of Acute Coronary Events

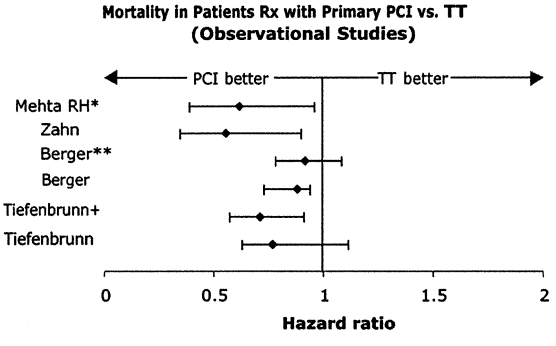

Figure 3. Outcomes of patients undergoing primary percutaneous coronary interventions versus intravenous fibrinolysis from observational studies. *In-hospital mortality; **for ideal patients; +combined in-hospital mortality and stroke in patients with acute myocardial infarction without shock. PCI = percutaneous coronary intervention; TT = thrombolytic therapy.

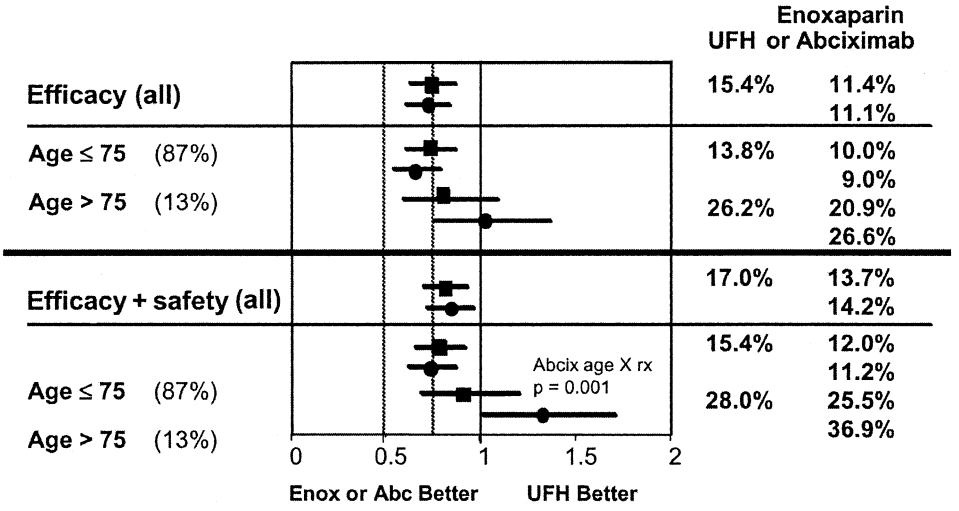

Figure 4. Thirty-day death, reinfarction, and recurrent angina in patients ≤75 years of age and in those >75 years of age treated with full-dose tenecteplase and enoxaparin (Enox) and half-dose teneteplase and full-dose abciximab (Abc) compared with those treated with full-dose abciximab and weight-adjusted unfractionated heparin (UFH).

who were eligible for reperfusion therapy. In this eligible cohort, 769 (26.7%) received thrombolysis, whereas 365 (12.7%) underwent primary PCI within 6 h of symptom onset. Patients treated with primary PCI had lower in-hospital mortality (14.4% vs. 17.6%; adjusted OR 0.62; 95% CI 0.39 to 0.96). Primary PCI was also associated with lower rates of reinfarction (1.0% vs. 5.7%; p = 0.003) and a trend toward lower rates of stroke (1.1% vs. 2.8%; p = 0.08). In contrast, there was a trend for higher major bleeding rates in the primary PCI group (8.6% vs. 5.9%; p = 0.09).

Stenting versus balloon angioplasty during primary PCI. No randomized clinical trial has evaluated primary coronary angioplasty versus stenting in elderly with STEMI. A subgroup analysis from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial has suggested that stent implantation during primary PCI is more effective in reducing the combined end point of death, recurrent myocardial infarction, disabling stroke, and/or ischemia-driven target vessel revascularization than balloon angioplasty alone in patients ≥65 years of age (OR 0.58; 95% CI 0.38 to 0.85) (31).

Emergency revascularization versus initial medical stabilization for elderly patients with cardiogenic shock complicating myocardial infarction. Patients with cardiogenic shock were specifically excluded from almost all randomized trials that compared primary PCI with intravenous thrombolysis and from the analysis of all observational studies evaluating the relative efficacy of the two reperfusion strategies. The SHOCK trial randomly assigned patients with shock due to left ventricular failure complicating myocardial infarction to emergency revascularization, either with PCI or coronary artery bypass grafting (n = 152), or to initial medical stabilization (n = 150) (32). While six-month mortality was lower in the revascularization group than in the medical therapy group (50.3% vs. 63.1%; p = 0.027), this benefit was only observed among patients age <75 years of age, not in those age ≥75 years, raising the question of whether there may be less benefit in the elderly.

In contrast, elderly patients with shock who were clinically selected in the nonrandomized SHOCK registry to undergo revascularization reported marked survival benefit compared with those that underwent late or no revascularization (33). Similarly, two other large registries demonstrated significant survival benefit in patients selected on the basis of physician's judgment for an invasive strategy (34,35). Thus, elderly with STEMI and shock require individualized consideration for revascularization (1).

ADJUNCTIVE THERAPIES DURING REPERFUSION IN ELDERLY WITH STEMI

As with reperfusion therapy, randomized clinical trials provide limited information on the risks and benefits of antithrombin agents (unfractionated or low-molecular-weight heparin or direct thrombin inhibitors [hirudin and its analogues]) or platelet glycoprotein IIb/IIIa receptor antagonists as adjunctive therapies during thrombolysis or mechanical reperfusion in elderly patients with STEMI. Subgroup analyses from some of these trials have provided insight into the merits versus risks of such adjunctive treatments.

Low-molecular-weight heparins. While no data are available on the use of low-molecular-weight heparin in elderly patients with STEMI undergoing primary PCI, subgroup analysis in the ASSENT-3 trial suggested similar benefits of low-molecular-weight heparin over weight-adjusted unfractionated heparin in reducing the 30-day composite of death, in-hospital reinfarction, refractory ischemia, intracranial hemorrhage, or major bleeding when given in combination with full-dose tenecteplase in patients with STEMI >75 years of age (Fig. 4) (36). However, in the ASSENT-3 PLUS trial, which compared enoxaparin with weight-

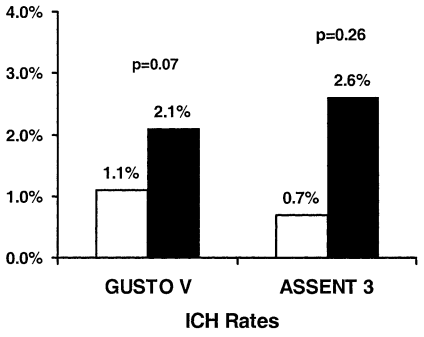

Figure 5. Risk of intracranial hemorrhage (ICH) in patients ≤75 years of age and in those age >75 years enrolled in Global Use of Strategies To Open occluded coronary arteries in acute myocardial infarction (GUSTO-V) and Assessment of Safety and Efficacy of a New Thrombolytic-3 (ASSENT-3) treated with half-dose thrombolytics and full-dose abciximab versus those treated with full-dose thrombolytics alone. **Open bars** = lytic; **solid bars** = lytic + glycoprotein IIb/IIIa.

adjusted unfractionated heparin in a prehospital setting, there was an unacceptably high risk of intracranial hemorrhage with enoxaparin in the elderly (2.2% vs. 0.97%; p = 0.047) (37). This may relate to an excessive dose of enoxaparin in the elderly population with decreased creatinine clearance, and underscores the importance of having sufficient data on appropriate doses of low-molecular-weight heparin in elderly populations to specifically evaluate risks and benefits.

Direct thrombin inhibitors. Similarly, no data are available on the risks/benefits of direct thrombin inhibitors in elderly patients with STEMI undergoing primary PCI. However, two trials reported the role of direct thrombin inhibitors among the elderly as an adjunct to thrombolysis in subgroup analysis (38,39). Antman et al. (38) compared hirudin with unfractionated heparin as adjunctive therapy to streptokinase or front-loaded tissue plasminogen activator, and suggested no advantage of this direct thrombin inhibitor over unfractionated heparin as an adjunct to thrombolysis in patients ≥65 years of age. Similarly, the Hirulog and Early Reperfusion/Occlusion-2 investigators reported no difference in 30-day mortality in patients ≥65 years of age with STEMI treated with bivalirudin or weight-adjusted unfractionated heparin as adjunct to streptokinase, but noted a trend toward lower in-hospital reinfarction in the bivalirudin-treated patients. However, there was also a trend toward higher intracranial hemorrhage in the patients ≥75 years of age treated with bivalirudin than in those receiving unfractionated heparin (1.0% vs. 0.5%; p = 0.16) (39).

Glycoprotein IIb/IIIa receptor antagonists. Data on the safety and efficacy of glycoprotein IIb/IIIa receptor antagonist together with half-dose thrombolytic therapy for patients with STEMI has been reported in subgroup analysis of two large-scale randomized clinical trials (36,40). The ASSENT-3 investigators reported that, in patients >75 years of age, there was a trend towards higher 30-day mortality in patients treated with the combination of tenecteplase and abciximab (22.3%) compared with those treated with tenecteplase and unfractionated heparin (15.9%) or tenecteplase and low-molecular-weight heparin (15.6%) (p = 0.11). Furthermore, the risk for major bleeding complications was threefold higher with full-dose abciximab and half-dose tenecteplase as compared with full-dose tenecteplase (2.6% vs. 0.7%) (Fig. 5) (36). Even though combination therapy had similar 30-day rates of composite of death, in-hospital reinfarction, or refractory ischemia in patients >75 years of age (efficacy end point, OR 1.02; 95% CI 0.76 to 1.36), the composite of efficacy plus safety end point (intracranial hemorrhage or major bleeding) was 30% higher in the combination therapy group (OR 1.30; 95% CI 1.01 to 1.68) (Figs. 4 and 5) (36). The GUSTO-V trial, which compared standard-dose reteplase versus half-dose reteplase with full-dose abciximab in patients with STEMI presenting within 6 h of symptom onset, showed no advantage of combination therapy in reducing the 30-day mortality among patients >75 years of age (18.3% vs. 17.9%; p = 0.83) (40). However, the risk of intracranial hemorrhage in patients >75 years of age was twice as high in the combination group as compared with the full-dose thrombolytic-treated patients (2.1% vs. 1.1%; p = 0.069) (Fig. 5).

In contrast with the increased risk of bleeding (and no difference in mortality) with glycoprotein IIb/IIIa receptor antagonists in combination with thrombolytic therapy (36,40), the subgroup analysis from the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up trial suggested no such increased risk of major bleeding with abciximab when used as an adjunct to stent implantation during primary PCI among patients >65 years of age (41). The 30-day (RR 0.30; 95% CI 0.09 to 0.99) and 6-month (RR 0.35; 95% CI 0.12 to 0.98) composite end points of death, reinfarction, or urgent target vessel revascularization were significantly lower in patients >65 years of age who received abciximab compared with placebo (41). No data exist on the benefits and risk of other glycoprotein IIb/IIIa receptor blockers as adjunct to chemical or mechanical reperfusion in the elderly.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

A suggested approach to reperfusion in elderly is shown in Figure 6. The optimal reperfusion strategy in this rapidly growing segment of the population remains to be established in large-scale randomized clinical trials. Until results of such trials are available, current data indicate that, when available, rapid primary PCI (preferably in a high-volume center) is particularly attractive as more elderly are eligible, and it improves reperfusion, reduces recurrent ischemia/infarction, and reduces the risk of intracranial bleeding as compared with thrombolytics in this cohort. In contrast, timely primary PCI is not available at most centers, and the risk of major bleeding (mainly at vascular access sites) is increased with PCI. In addition, the risk of renal failure remains an important concern with primary PCI. While

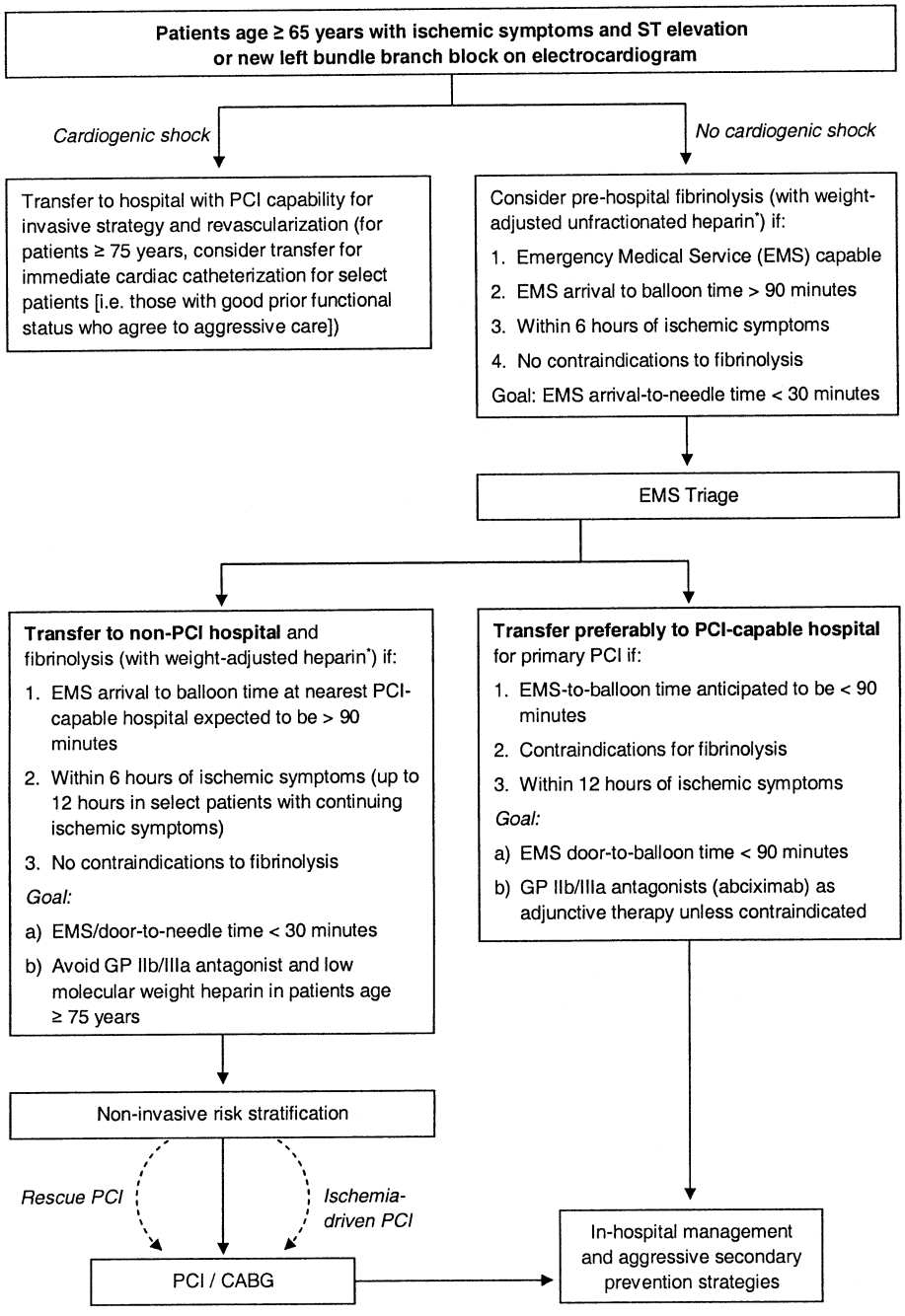

Figure 6. Recommended approach to reperfusion therapy for patients age ≥65 years with ST-segment elevation myocardial infarction. *Dose of weight-adjusted unfractionated heparin = 60 U/kg bolus (maximum 4,000 U) followed by infusion at 12 U/kg/h (maximum dose 1,000 U/h). CABG = coronary artery bypass grafting; EMS = emergency medical service; GP = glycoprotein; PCI = percutaneous coronary intervention.

primary PCI may be considered the reperfusion strategy of choice for elderly patients with STEMI in high-volume hospitals that can achieve rapid time to reperfusion, the proven benefits of thrombolytic therapy should prompt wider use in the elderly in most centers where rapid primary PCI is not available. Efficient systems of transfer may provide the opportunity for wider use of primary PCI, especially for patients with contraindications to thrombolysis.

Based on the studies presented, should all elderly patients with STEMI who present to hospitals where primary PCI is unavailable be transferred immediately to centers that offer it? The inherent time delay in the transfer of patients for primary PCI may offset the relative time-sensitive benefits of reperfusion with this strategy. Rapid initiation of thrombolysis should be considered in these elderly patients in whom timely mechanical reperfusion is not feasible. In no other cohort is the concept of net clinical benefit (mortality benefit weighed against the risk of hazard) of thrombolysis more important than in the elderly. Therapy and choice of

agents (fibrin-specific vs. nonspecific agents) should be individualized and based on the risk of mortality and the risk of stroke estimated using published models (1–3,11,12). Preliminary data support the use of weight-based fibrin-specific agent tenecteplase with weight-adjusted heparin as utilized in the ASSENT-3 trials among this age group (36). Current national guidelines for STEMI management designates class III indication to the concomitant use of glycoprotein IIb/IIIa antagonist and low-molecular-weight heparin with fibrinolytic therapy in patients with STEMI > 75 years and should be avoided in this age group (1). Reduction in the dose of heparin in older patients, as suggested in the preceding text, and close and early monitoring of anticoagulation activity may be beneficial in reducing the risk of intracranial hemorrhage and major bleeding as well as in improving survival in elderly patients receiving fibrinolysis. Recent trials have reported extremely low rates of intracranial hemorrhage (0.5% to 1.1%) among elderly patients with proper patient selection, weight-adjusted heparin dosing, and close early monitoring of anticoagulation activity (36,37,39).

Decisions regarding transfer after thrombolysis can be based on the clinical course of individual patients. A newer strategy, currently under investigation, is one of facilitated PCI, wherein a patient receives half-dose thrombolytic therapy with full-dose glycoprotein IIb/IIIa inhibitor, followed by rapid transfer to a hospital where PCI can be performed. Studies that have evaluated facilitated PCI have not reported any data on the benefits and risk of this treatment strategy in the elderly (42,43). Given the unacceptably high risk of such combination therapy in the elderly in trials to date, it remains to be established in future trials if the strategy of facilitated PCI would be a good option for the elderly.

Clearly targeted large-scale clinical trials are needed to evaluate the relative merits of the available reperfusion strategies (immediate primary PCI, transfer for primary PCI even when a significant delay is anticipated during transfer, thrombolysis, or facilitated PCI) as well as adjunctive therapies (low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, and direct thrombin inhibitors) in the elderly with STEMI. Avoiding selection bias and assuring inclusion of substantial proportions of older patients in most randomized clinical trials may further our understanding regarding the optimal reperfusion strategy in this cohort. Finally, prospective and retrospective registries including the elderly with STEMI are needed to define patterns of care, and may help to refine our understanding of a number of issues that remain unanswered regarding reperfusion in the elderly.

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REFERENCES

1. Antman E, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 Guidelines for Management of Acute Myocardial Infarction). 2004. Available at: www.acc.org/clinical/guidelines/stemi/index.pdf. Accessed June 10, 2004.
2. Mehta RH, Rathore, SS, Wang Y, et al. Acute myocardial infarction in the elderly: differences by age. J Am Coll Cardiol 2001;38:736–41.
3. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1,000 patients. Lancet 1994;343:311–22.
4. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. JAMA 1992;268:1417–22.
5. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials. Lancet 2003;361:13–20.
6. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–82.
7. Gruppo Italiano per lo Studio della Sopravvivenza nel'Infarto Miocardico. GISSI-2: a factorial randomized trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. Lancet 1990;336:65–71.
8. Third International Study of Infarct Survival Collaborative Group. ISIS-3: a randomized comparison of streptokinase vs. tissue plasminogen activator vs. anistreplase and aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 1992;339:753–70.
9. Rogers WJ, Bowlby LJ, Chandra NC, et al. Treatment of myocardial infarction in the United States (1990 to 1993). Observations from the National Registry of Myocardial Infarction. Circulation 1994;90:2103–14.
10. Rathore SS, Mehta RH, Wang Y, et al. Age and quality of care provided to elderly patients with acute myocardial infarction. Am J Med 2003;114:307–15.
11. Simoons ML, Maggioni AP, Knatterud G, et al. Individual risk assessment for intracranial hemorrhage during thrombolytic therapy. Lancet 1993;342:1523–8.
12. Brass LM, Lichtman JH, Wang Y, et al. Intracranial hemorrhage associated with thrombolytic therapy for elderly patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. Stroke 2000;31:1802–11.
13. White HD. Thrombolytic therapy in the elderly. Lancet 2000;356:2028–30.
14. White HD, Barbash GI, Califf RM, et al. Age and outcome with contemporary thrombolytic therapy. Results from the GUSTO-I trial. Circulation 1996;94:1826–33.
15. Van de Werf F, Barron HV, Armstrong PW, et al. Incidence and predictors of bleeding events after fibrinolytic therapy with fibrin-specific agents: a comparison of TNK-tPA with rt-PA. Eur Heart J 2001;22:2253–61.
16. Curtis JP, Alexander JH, Huang Y, et al. Efficacy and safety of two unfractionated heparin dosing strategies with tenecteplase in acute myocardial infarction (results from Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-2 and -3). Am J Cardiol 2004;94:279–83.
17. Thiemann DR, Coresh J, Schulman SP, et al. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. Circulation 2000;101:2239–46.
18. Angeja BG, Rundle AC, Gurwitz JH, et al., for the Participants in the National Registry of Myocardial Infarction. Death or nonfatal stroke in patients with acute myocardial infarction treated with tissue plasminogen activator. Participants in the National Registry of Myocardial Infarction-2. Am J Cardiol 2001;87:627–30, A9.
19. Soumerai SB, McLaughlin TJ, Ross-Degnan D, et al. Effectiveness of thrombolytic therapy for acute myocardial infarction in the elderly: cause for concern in the old-old. Arch Intern Med 2002;161:561–8.

20. Gitt AK, Zahn R, Weinberger H, et al. Thrombolysis for acute myocardial infarction in patients older than 75 years: lack of benefit for hospital mortality but improvement of long-term mortality: results of the MITRA and MIR registries (abstr). J Am Coll Cardiol 2001;37 Suppl A:648A.
21. Berger AK, Radford MJ, Wang Y, et al. Thrombolytic therapy in older patients. J Am Coll Cardiol 2000;36:366–74.
22. Stenestrand U, Wallentin L, for the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS HIA). Fibrinolytic therapy in patients 75 years and older with ST-segment-elevation myocardial infarction: one-year follow-up for large prospective cohort. Arch Intern Med 2003;163:965–71.
23. Grines CL, Browne KF, Marco J, et al., for the Primary Angioplasty in Myocardial Infarction Study Group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673–9.
24. The GUSTO-IIb Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997;336:1621–8.
25. Zijlstra F, Patel A, Jones M, et al. Clinical characteristics and outcome of patients with early (<2 h), intermediate (2–4 h) and late (>4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction. Eur Heart J 2002;23:550–7.
26. de Boer MJ, Ottervanger JP, van't Hof AW, et al., for the Zwolle Myocardial Infarction Study Group. Reperfusion therapy in elderly patients with acute myocardial infarction: a randomized comparison of primary angioplasty and thrombolytic therapy. J Am Coll Cardiol 2002;39:1723–8.
27. Berger AK, Shulman KA, Gersh BJ, et al. Primary coronary angioplasty vs thrombolysis for the management of acute myocardial infarction in elderly patients. JAMA 1999;282:341–8.
28. Zahn R, Schiele R, Schneider S, et al. Primary angioplasty versus intravenous thrombolysis in acute myocardial infarction: can we define subgroups of patients benefiting most from primary angioplasty? Results from the pooled data of the Maximal Individual Therapy in Acute Myocardial Infarction registry and the Myocardial Infarction registry. J Am Coll Cardiol 2001;37:1827–35.
29. Tiefenbrunn AJ, Chandra NC, French WJ, et al. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction. A report from the Second National Registry of Myocardial Infarction (NRMI-2). J Am Coll Cardiol 1998;31:1240–5.
30. Mehta RH, Sadiq I, Goldberg RJ, et al., for the GRACE Investigators. Effectiveness of primary percutaneous coronary intervention compared with that of thrombolytic therapy in elderly patients with acute myocardial infarction. Am Heart J 2004;147:253–9.
31. Stone GW, Grines CL, Cox DA, et al., for the CADILLAC Investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957–66.
32. Hochman JS, Sleeper LA, Webb JG, et al., for the SHOCK Investigators. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625–34.
33. Dzavik V, Sleeper LA, Cocke TP, et al., for the SHOCK Investigators. Early revascularization is associated with improved survival in elderly patients with acute myocardial infarction complicated by shock: a report of SHOCK trial registry. Eur Heart J 2003;24:828–37.
34. Dauerman HL, Goldberg RJ, Malinski M, et al. Outcomes and early revascularization for patients greater than or equal to 65 years of age with cardiogenic shock. Am J Cardiol 2001;87:844–8.
35. Dauerman HL, Ryan TJ, Piper WD, et al. Outcomes of percutaneous coronary intervention among elderly patients in cardiogenic shock: a multicenter decade-long experience. J Invasive Cardiol 2003;15: 380–4.
36. ASSENT-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomized trial in acute myocardial infarction. Lancet 2001;358:605–13.
37. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the ASSENT-3 PLUS randomized trial in acute myocardial infarction. Circulation 2003;108:135–42.
38. Antman EM. Hirudin in acute myocardial infarction: the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. Circulation 1996;94:911–21.
39. The HERO-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction. Lancet 2001;358:1855–63.
40. The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition. Lancet 2001;357:1905–14.
41. Montalescot G, Barragan P, Wittenberg O, et al., for the ADMIRAL Investigators. Platelet glycoprotein IIb-IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344: 1895–903.
42. Herrman HC, Moliterno DJ, Ohman EM, et al. Facilitation of early coronary intervention after reteplase with or without abciximab in acute myocardial infarction. Results from SPEED (GUSTO-4) trial. J Am Coll Cardiol 2000;36:1489–96.
43. Kastrati A, Mehilli J, Schlotterbeck K, et al. Early administration of reteplase with abciximab vs abciximab alone in patients with acute myocardial infarction referred for percutaneous coronary interventions: a randomized trial. JAMA 2004;291:947–54.